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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/500,397	02/08/2000	Gerald Soff	4228-1-1-1	2549

7590 08/18/2003

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EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	22

DATE MAILED: 08/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No. 09/500,397	Applicant(s) SOFF ET AL.	
	Examiner MINH-TAM DAVIS	Art Unit 1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 17 April 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 6 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *17 April 2003*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See attached*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *none*.

   Claim(s) objected to: *none*.

   Claim(s) rejected: *19-21, 23-24, 76-90 for reasons already of record*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant adds new claims 76-90, which are related to claims 19-21, 23-24 and are not new matters.

Accordingly, claims 19-21, 23-24, 76-90 are being examined.

It is noted that this application still contains claims drawn to an invention nonelected with traverse in Paper No.9. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The following are the remaining rejections.

OBVIOUSNESS DOUBLE PATENTING

It is noted that new claims 76-78, 80-87 would be included with claims 19-20, 23 as being provisionally rejected under obviousness type double patenting over claims 1-14 of Application No:08/991761, now patented, US 6,576,609 B1.

However, similar to the previous rejection of claims 19-20, 23, this rejection however will be hold in abeyance until the time of allowance, if the claims are allowable, as previously requested for claims 19-20, 23 by Applicant.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

Rejection under 35 USC 112, first paragraph, of claims 19-21, 23-24 pertaining to lack of enablement for a method for treating any angiogenic disease remains for reasons already of record in paper No.18. New claims 76-77, 79-86, 88-90 are rejected for the same reasons already of record.

Applicant argues that Berman et al do not administer a "therapeutically effective amount" of plasminogen activator that increases the amount of angiostatin in the animal. Berman injects 20 ul aliquots of urokinase intrastromally into the corneas of rabbits.

Applicant further asserts that Gately et al, 1996, have shown that angiostatin inhibits angiogenesis in corneas. Applicant concludes that Berman et al do not use the claimed method.

Applicant asserts that in Application SN 08/991761, which had been patented, the Examiner has agreed to the following facts in the Supplemental Declarations by Soff et al: 1) Urokinase alone generates angiostatin in human plasma, 2) Urokinase alone generates angiostatin in human patients, 3) the generation of angiostatin has a clinical benefit in human patients with malignant neoplastic disease, and 4) when administered without a sulfhydryl donor, the dose and dosage regimen of plasminogen activator can be adjusted to generate levels of angiostatin that have a clinical benefit in patients with malignant neoplastic disease.

Applicant further argues that the Examiner has not supplied any evidence or reason to doubt that the generation of angiostatin in patients would like wise have a clinical benefit in other angiogenic diseases.

The recitation of Gately et al is acknowledged.

Applicant's arguments set forth in paper No.21 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that although Applicant has shown that angiostatin could be detected in cancer patients, after urokinase is administered, Applicant has not shown that angiostatin could be generated after administering urokinase in a patient having any angiogenic disease, because different diseases have different characteristics and properties, and it is unpredictable that patients with different diseases would have the same responses to the same drug.

Moreover, even if angiostatin could be detected in patients with any type of angiogenic diseases, it is unpredictable that administrating of urokinase would not cancel any effect by angiostatin. Berman et al teach that administration of a plasminogen activator, urokinase, actually promotes vascularization in the cornea *in vivo*. Thus the effect of urokinase seems to be opposite to the effect of angiostatin, and it is unpredictable that administrating of urokinase would not cancel any effect by angiostatin, if angiostatin is produced *in vivo* by administration of urokinase.

Further, it is noted that the level of angiostatin detected in plasma of cancer patient treated with urokinase is barely noticeable in a Western blot in figure 17A, and that the level of angiostatin needed to inhibit a neovascular response to a hydron pellet *in vivo* as shown in figure 5B is 10 ug/ml. Thus even if angiostatin could be detected in patients with any type of angiogenic diseases, it is unpredictable that said level is adequate for effective treatment of any type of angiogenic diseases, nor is it predictable

that the level of angiostatin could be elevated such that it is adequate for treating any type of angiogenic disease, because different diseases have different characteristics and properties, and it is unpredictable that patients with different diseases would have the same responses to the same drug. The specification however does not disclose any guidance concerning whether angiostatin is detected in patients having any type of angiogenic disease when treated with urokinase, and which level of angiostatin is adequate for treating any type of angiogenic disease, including various angiogenic diseases disclosed in claims 89-90.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

August 13, 2003